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A COMPREHENSIVE STUDY ON INTERACTION OF ANTIMICROBIAL PEPTIDES AS A TREATMENT OF TUBERCULOSIS

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Abstract:

Introduction: Mycobacterium tuberculosis *(Mtb) are classified as acid-fast Gram-positive bacteria due to their lack of a typical outer cell membrane. Contagious tuberculosis spreads through the air.* ***Objectives of the study****: The main objective of the study is to analyze the interaction of antimicrobial peptides as a treatment of tuberculosis.* ***Methodology of the study:*** *This cross-sectional study was conducted at Services Hospital Lahore during February 2018 till July 2018. The data was collected from 100 patients of both genders. Those patients who suffered from TB and visited the OPD of the hospital included in this study. In this analyzes we compare the different drugs of TB which are available in the market as compared to antimicrobial peptides. A reasonable approach to find new therapeutics against the high number of MDR and XDR strains is to find molecules having a different killing mechanism.* ***Results:*** *The data was collected from 100 TB patients. The mean age of the selected patients was 50.98±4.56 years. Peptide concentrations of 1, 10 and 100 µg/ml, 10-fold serial concentrations were used. After 7 days incubation with peptides, the CFU/ml of each sample was calculated compared with day 0. The samples treated with D1 or D5 at 100 µg/ml had dramatic reductions in CFU/ml. eptide D5 increased the anti-tuberculosis activity by about 5.7-fold compared to D4, which is due to a valine to lysine substitution at position 16.* ***Conclusion:*** *It is concluded that Many AMPs have good or moderate activities against mycobacteria, however, in general the activities are lower as compared to the activities found against other Gram-negative or Gram-positive bacteria.*

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INTRODUCTION:

Mycobacterium tuberculosis (Mtb) are classified as acid-fast Gram-positive bacteria due to their lack of a typical outer cell membrane. Contagious tuberculosis spreads through the air. According to World Health Organization's report: more than 2 billion people, one-third of the world's population, are infected with M. tuberculosis [1]. In 2008, 9.4 million new cases of tuberculosis (TB) were reported including 1.4 million cases among people living with human immunodeficiency virus (HIV). There were 1.8 million people who died from TB in 2008, including 500,000 people with HIV [2]. TB is a leading killer of HIV patients. 5% of all TB cases involve multi-drug resistant (MDR) Mtb, which is a form of Mtb that is difficult and expensive to treat and fails to respond to standard first-line drugs [3]. The emergence and rapid spread of MDR Mtb strains represents a worldwide health care problem. M. tuberculosis within host cells is surrounded by a capsule outside the bacterial wall and membrane which represents a passive barrier impeding the diffusion of molecules towards inner parts of the envelope. The capsule consists of a complex mixture of polysaccharides, proteins, lipids and enzymes including pro-teases and lipidases all of which may participate to the active resistance of the bacterium to the hosts' microbicidal mechanisms [4]. Since, the lipid-rich cell wall structure of mycobacteria makes the cell surface hydrophobic, the permeability to anti-tuberculosis drugs is reduced. It is believed that the resistance to anti-mycobacterial drugs is mainly due to the peculiar properties of the mycobacterial cell envelope [5].

Tuberculosis (TB) is still one of the most deadliest communicable diseases worldwide. In 2013, an estimated 9 million people developed TB and 1.5 million people died from TB. The global trend is a decrease of incidence, prevalence, and mortality. However, with the emergence of multi-drug resistant (MDR) and extensively drug resistant (XDR) Mycobacterium tuberculosis (Mtb) strains, new classes of anti-mycobacterial agents are urgently needed. MDR strains are resistant at least against isoniazid (INH) and rifampicin (RIF) and XDR strains are resistant against INH, RIF, fluoroquinolone, and one of amikacin, kanamycin, or capreomycin [6].

Objectives of the study

The main objective of the study is:

- To analyze the interaction of antimicrobial peptides as a treatment of tuberculosis.

METHODOLOGY OF THE STUDY:

This cross sectional study was conducted at Services Hospital Lahore during February 2018 till July 2018. The data was collected from 100 patients of both genders. Those patients who suffered from TB and visited the OPD of the hospital included in this study. In this analyzes we compare the different drugs of TB which are available in the market as compared to antimicrobial peptides. A reasonable approach to find new therapeutics against the high number of MDR and XDR strains is to find molecules having a different killing mechanism. On the other hand, the assays as well as the conditions used are quite diverse. All the collected data was analyzed using SPSS version 21.0.

RESULTS:

The data was collected from 100 TB patients. The mean age of the selected patients was 50.98±4.56 years. Peptide concentrations of 1, 10 and 100 µg/ml, 10-fold serial concentrations were used. After 7 days incubation with peptides, the CFU/ml of each sample was calculated compared with day 0. The samples treated with D1 or D5 at 100 µg/ml had dramatic reductions in CFU/ml. eptide D5 increased the anti-tuberculosis activity by about 5.7-fold compared to D4, which is due to a valine to lysine substitution at position 16. Our lead compound, peptide D1 had a 2.8-fold improvement in anti-tuberculosis activity compared to that of D4.

Table 01: Biological Activity of peptides against M. tuberculosis

Peptide Name	Hemolytic Activity		Anti-Tuberculosis Activity to H37Rv Strain		Therapeutic Index to H37Rv Strain		Anti-Tuberculosis Activity to MDR Strain
	HC_{50}[a] µg/ml	Fold[b]	MIC[c] µg/ml	Fold[b]	HC_{50}/MICd	Fold[b]	MIC[c] µg/ml
D1	421.5	120	70.7	2.8	6.0	333	57
D2	83	24	83.7	2.4	1.0	56.0	72
D3	14	4	109.2	1.8	0.13	7.2	100
D4	3.5	1	200	1.0	0.018	1.0	I[e]
D5	47	13	35.2	5.7	1.3	72.0	49
L-LL37	43.5	12	I[e]	—	I[e]	—	I[e]
D-LL37	125	36	200	1.0	0.63	35.0	I[e]

DISCUSSION:

Several of the peptides designed from first principles had improved activity relative to LL37. In our studies we observed that only D-LL37 exhibits growth inhibitory activity against H37Rv, but does not appear to kill M.tuberculosis at concentration below 100 µg/mL. Careful examination of data from others reveals that our results with L-LL37 are consistant with previous studies. Lactoferricins are naturally occurring peptides, formed by the cleavage of the highly cationic N1 terminal domain of the iron-binding protein lactoferrin [7]. All peptides showed an antimycobacterial activity with LD50 values between 10 and 40 µM. The stronger activity was found in the bovine-based peptides. A significant difference in the activity against three different M. avium strains could not be found [8].

PR-39, a proline–arginine rich AMP isolated from pig intestine, has activity against drug-susceptible as well as MDR clinical isolates of Mtb. At 50 µg/ml 80% growth inhibition of Mtb H37Rv could be achieved. Martineau et al. investigated the role of iron concentration on the activity of lipocalin 2. Lipocalin 2–induced suppression of Mtb CFU was greater in iron-depleted broth than in iron-replete broth (150 µM Fe) with values of 60% versus 45%, respectively [9]. Azurophil granule protein (AZP) are active against M. smegmatis and M. bovis BCG [73]. Jena et al. investigated this mixture of molecules and identified elastase and lysozyme to be important for mycobacterial killing [10].

CONCLUSION:

It is concluded that Many AMPs have good or moderate activities against mycobacteria, however, in general the activities are lower as compared to the activities found against other Gram-negative or Gram-positive bacteria. One big advantage of AMPs is that the active ones showed almost same activities against Mtb strains being sensitive against conventional antibiotics and also against MDR and XDR strains.

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